REMARKS

Claims 1-7 and 10-13 are pending. No claim is being amended at this time. The foregoing listing of the claims is provided for the convenience of the Office.

Claims 1-7 remain rejected and claims 11 and 12 are rejected under 35 U.S.C. § 103(a) for allegedly being unpatentable over **"Muller et al. (WO 2003/066031) in view of Uekama et al. ("Cyclodextrin Drug Carrier Systems," Chem. Rev. 1998, 98, pp 2045, 2048 (Table 2); and 2063),** wherein US 2005/0085445 is being used as the English language equivalent of WO 2003/066031" (Office Action, page 4, bold emphasis in original). The rejection states, in part (Office Action, page 6):

> An ordinary skilled artisan would have had a reasonable expectation of obtaining HFA/drug/acylated drug formulations, because HFA/drug/hydroxypropyl cyclodextrin/drug formulations are known to be suitable and both hydroxypropyl cyclodextrin and the acylated cyclodextrins tested by Uekama are soluble in ethanol.

This is respectfully traversed.

[1] Claim 1 is directed to an HFA drug formulation that includes a partially or fully acylated alpha (α), beta (β) or gamma (γ) cyclodextrin.

[2] Muller

Muller et al concerns metered-dose aerosol inhaler stabilised pharmaceutical HFA suspension formulations comprising a native or modified cyclodextrin. There is no disclosure of acylated cyclodextrins. Rather, Muller focuses heavily on hydroxyalkyl modified cyclodextrins; see Muller at page 2, paragraph 0024:

> The cyclodextrine used according to the invention can be a native or modified α-, β-, or γ-cyclodextrine. Examples of modified cyclodextrines are hydroxymethyl-α-cyclodextrine, hydroxyethyl-α-cyclodextrine, hydroxypropyl-α-cyclodextrine,

> α-cyclodextrine butyl sulphonate, α-cyclodextrine butyl fluoride and sulphobutyl-α-cyclodextrine; hydroxymethyl β-cyclodextrine, hydroxyethyl-β-cyclodextrine, hydroxypropyl-β-cyclodextrine, β-cyclodextrine butyl sulphonate, β-cyclodextrine butyl fluoride and sulphobutyl-α-cyclodextrine as well as hydroxymethyl-γ-cyclodextrine, hydroxyethyl-γ-cyclodextrine, hydroxypropyl-γ-cyclodextrine, γ-cyclodextrine butyl sulphonate, γ-cyclodextrine butyl fluoride and sulphobutyl-γ-cyclodextrine.

In fact, Muller appears to use hydroxyalkylated cyclodextrins in **all** of his exemplified formulations.

[3] Uekama

Uekama is a review article entitled "Cyclodextrin Drug Carrier Systems." Uekama describes cyclodextrin derivatives (including acylated cyclodextrins); however, Uekama does not refer at all to formulations that are to be delivered to the lung *via* an inhaled aerosol composition (*cf*: Muller discussion above).

Uekama discloses a table ("Table 1" in Uekama at page 2047) that includes "[t]ypical examples of the pharmaceutically useful β-cyclodextrin derivatives" (Uekama, page 2046). In Uekama's Table 1, the derivatives are "classified into hydrophilic, hydrophobic, and ionic derivatives" (Uekama, page 2046). "Hydroxyalkylated cyclodextrins," i.e., the type of cyclodextrin that is used in all of Muller's exemplified formulations, are classified by Uekama as "**hydrophilic** derivatives" (see Uekama's Table 1 at page 2047, emphasis added). On the other hand, "acylated cyclodextrins," which are required by the present claims, are classified by Uekama as "**hydrophobic** derivatives" (see Uekama's Table 1 at page 2047, emphasis added).

[4] The Supreme Court discussed the requirements for making rejections under 35 U.S.C. 103 in *KSR Intern. Co. v. Teleflex Inc.* 127 S.Ct. 1727, 1742 (2007, bolded, underline emphasis added).

> Often, it will be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person

having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. To facilitate review, this analysis should be made explicit. *See In re Kahn*, 441 F.3d 977, 988 (C.A.Fed.2006) ("[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness"). As our precedents make clear, however, the analysis need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ.

When it first established the requirement of demonstrating a teaching, suggestion, or motivation to combine known elements in order to show that the combination is obvious, the Court of Customs and Patent Appeals captured a helpful insight. See *Application of Bergel*, 48 C.C.P.A. 1102, 292 F.2d 955, 956-957 (1961). As is clear from cases such as Adams, **a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art**. Although common sense directs one to look with care at a patent application that claims as innovation the combination of two known devices according to their established functions, **it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does**. This is so because **inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known**.

Thus, a claim is not proved obvious merely by showing that the elements of that claim can be found in the prior art. Rather, the Office must articulate some reason as to why a person of ordinary skill in the art, at the time of the invention, would have combined the elements in the manner required by the claim.

[5] Here, claim 1 is directed to an HFA drug formulation that includes a partially or fully acylated alpha (α), beta (β) or gamma (γ) cyclodextrin. As explained in the specification, an HFA (hydro fluoro alkanes) or mixtures thereof, are used, e.g., as propellants in inhalation delivery devices (e.g., pressure metered dose inhalers).

Muller et al concerns metered-dose aerosol inhaler stabilised pharmaceutical HFA suspension formulations comprising a native or modified cyclodextrin. There is no disclosure of

acylated cyclodextrins (see paragraph 0024 on page 2 of Muller) in Muller. Muller focuses heavily on hydroxyalkyl modified cyclodextrins, which according to Uekama, are **hydrophilic** in nature. In fact, Muller appears to use hydroxyalkylated cyclodextrins in **all** of his exemplified formulations. Further, Muller's disclosure relates solely to inhaled formulations, it does not concern any other type of formulation.

Uekama et al concerns cyclodextrin drug carrier systems. Acylated cyclodextrins are disclosed in Tables 1 and 2 on pages 2047 and 2048. It is to be noted that in Table 1 the acylated cyclodextrins are under the heading of 'Hydrophobic Derivatives'. Uekama discloses formulations that can be administered orally, rectally, nasally, ocularly and dermally (see Uekama at pages 2056-9).

When discussing nasal delivery, Uekama mentions 'water-soluble cyclodextrin complexes' (line 2 of the Nasal Delivery section on page 2057) and all the cyclodextrins discussed in this section of Uekama are **hydrophilic**. Thus, the skilled artisan is not taught about the inclusion of a hydrophobic cyclodextrin in a formulation for nasal delivery. The last sentence of the 'Nasal Delivery' section of Uekama mentions that the potential of cyclodextrins to improve the pulmonary delivery of drugs has been evaluated. As this is in the same paragraph and section of Uekama where only hydrophilic cyclodextrins have been discussed and exemplified, **the skilled artisan is again not taught about the inclusion of a hydrophobic cyclodextrin in a pulmonary formulation**.

The formulation of Muller is for administration to the respiratory tract (line 4 of [0004]), i.e., pulmonary delivery. Given what is disclosed in Uekama about this form of delivery, it is submitted that nothing in the prior art of record would have led one to combine the disclosure of Muller and Uekama in the manner suggested by the Office.

Thus, the Office has only identified elements of the present claims in two disclosures, but has not articulated any reason why one would have combined these two disclosures in the manner suggested by the Office. Applicants respectfully request reconsideration and withdrawal of the rejection for at least this reason.

[6] Applicants respectfully request that the rejection be reconsidered and withdrawn for the following additional and independent reason. As explained above, Muller focuses heavily on hydroxyalkyl modified cyclodextrins, which according to Uekama, are **hydrophilic** in nature. In fact, Muller appears to use hydroxyalkylated cyclodextrins in **all** of his exemplified formulations. In contrast, the claims require the presence of acylated cyclodextrins, which according to Uekama, are **hydrophobic** in nature. Mere fact that these two **different** types of cyclodextrins happen to have solubility in ethanol (Office Action, page 6, *supra*) would **not** have led one to ignore outright Muller's clear preference for hydrophilic cyclodextrins and turn to hydrophobic cyclodextrins, much less turn to the partially or fully acylated alpha (α), beta (β) or gamma (γ) cyclodextrins of the present claims. If anything, the teachings of Muller and Uekama would have led one of ordinary skill in the art away from making the modifications needed to arrive at the claimed formulations.

[7] Finally, the drug formulations of the present claims are useful for pulmonary or nasal delivery (see, e.g., page 2 lines 20-21 of the present application). There is nothing in the prior art of record, given in particular what is disclosed in Muller and Uekama about the above-mentioned forms of delivery, that would have led one to include a partially or fully acylated cyclodextrin (which are examples of hydrophilic cyclodextrins) in a formulation for pulmonary or nasal delivery. As such, there is nothing in the prior art of record that would have led one to combine the disclosure of Muller and Uekama in the manner suggested by the Office. Applicants respectfully request reconsideration and withdrawal of the rejection for this additional and independent reason.

[8] In summary, Applicants therefore respectfully request that the rejection be reconsidered and withdrawn because the Office, at most, has only identified the elements of the present claims in three unrelated disclosures, but has not articulated any reason why the claimed kits and pharmaceutical compositions would have been obvious at the time that the present application was filed.

Applicants submit that all claims are in condition for allowance.

The fee in the amount of $1,110 is being paid concurrently on the Electronic Filing System (EFS) by way of a Deposit Account authorization. Please apply any other charges or credits to deposit account 06-1050, referencing Attorney Docket No. 06275-0512US1 / 101287-1P US/R&I.

Respectfully submitted,

Date: November 8, 2010

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